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HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
ETHYLENE GLYCOL DIACETATE
(CAS NO.: 111-55-7)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for ethylene glycol diacetate (EGD; CAS NO.: 111-55-7) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use both the existing data on EGD in conjunction with data from ethylene glycol (a structural surrogate) and EPA-acceptable predictive computer models to adequately fulfill all the Screening Information Data Set (SIDS) endpoints. We believe that in total these data are adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests. Furthermore, they follow the principles contained in the letter the EPA sent to all HPV Challenge Program participants on October 14, 1999 in which participants are directed to maximize the use of existing data for scientifically appropriate related chemicals in order to minimize animal testing.

Ethylene glycol diacetate is colorless low odor, very slow-evaporating liquid that is manufactured to a high degree of purity. This chemical finds its major use in thermoplastic acrylic coatings as a re-flow solvent and as an industrial intermediate as a slow release acetic acid source in silicate foundry core-binding applications. It is also used as a solvent in some printing inks. At this time the ACGIH has not established any industrial work place exposure levels for this chemical.

JUSTIFICATION FOR USE OF SURROGATE DATA

As a means to reduce the number of tests that may be conducted, the EPA allows for the use of categories or surrogate chemicals to group together chemicals that are structurally similar to characterize specific SIDS endpoints (USEPA 1999a). Accordingly, for the completion of some endpoints for ethylene glycol diacetate (EGD) this test plan utilizes data from ethylene glycol (EG) as a surrogate chemical. The toxicity of EGD to mammalian species is strongly believed to be a result of its metabolic conversion to EG by cleavage of the ester bonds. Chemicals held together through ester bonds are often readily split into the parent alcohol and acid moieties in biological systems through the action of various esterase enzymes that are located through out the body including the mucosal surfaces of the respiratory tract.

While anecdotal in nature, the clinical symptoms detailed in the Hazardous Substances Data Base (HSDB) following a toxicosis in humans with EGD is consistent with what occurs after a toxic exposure to EG. These include "1. Central nervous depression characterized by transient exhilaration, drunkenness, ataxia, and vertigo, progressing to stupor and finally coma, with or without a transient period of convulsions. 2. Death from respiratory arrest or perhaps cardiovascular collapse. 3. Nausea, vomiting, abdominal pain, dehydration, weakness, muscle tenderness. 4. Hyperpnea may indicate either metabolic acidosis or pulmonary edema. 5. Carpopedal spasm or other signs of hypocalcemic tetany. 6. Lumbar pain, albuminuria, hematuria, oliguria progressing to anuria. 7. Acute renal failure with uremia, peripheral edema, ascites, pulmonary edema, drowsiness, cyanosis, coma, and death in 7 to 10 days. This observation lends further support to the hypothesis that EGD is metabolized to EG in humans and is most likely the etiological basis of its toxicity.

At this time, although there are no pharmacokinetic data detailing the actual rates at which EGD metabolizes into EG, there are such data available on several other types of similar compounds formed by ester linkages. These data demonstrate that the ester bond between an acetic acid and an alcohol is readily and rapidly cleaved and that the primary driver for systemic toxicity is the parent alcohol/glycol (the formation of the acetate ion often leads to irritation in nasal epithelial tissues under conditions of respiratory exposure). Examples of such molecules include methyl acetate, ethyl acetate and butyl acetate whose toxicity following exposure is well recognized to be due to the metabolic formation of the respective alcohol. Similarly, with glycol-ether acetate molecules the basis for toxicity is the glycol-ether parent. Examples of this include, the reproductive toxicity seen following exposure to ethylene glycol methyl ether (EGME) and ethylene glycol ethyl ether (EGEE) is also manifested following an exposure to their acetylated moieties (EGME-acetate and EGEE-acetate). Studies found in the literature have also demonstrated the formation of oxalic acid formation (a known EG metabolite) following exposure to EG-monoacetate. Since EGD is structurally similar to these aforementioned molecules, it is scientifically plausible to assume EGD will also be metabolized to EG.

Probably the most definitive of all the evidence supporting the supposition that EGD is cleaved into EG, which dictates its toxicity, is found in the results of repeat exposure studies conducted on EGD (see robust summary section). In one of the studies, it is reported that the kidneys of a rat that died after one week of exposure to EGD were filled with calcium oxalate crystals. The histological appearance of the kidneys were indistinguishable from test animals that had received EG alone in the same study. In a second EGD exposure study, it was noted that 4 of 11 animals that died between Days 7 and 114, and 4 of the remaining 7 animals all had renal lesions that were associated with the presence of calcium oxalate crystals. These kidney lesions were also histologically similar to renal lesion from an exposure to EG. The identification of oxalate crystals in the urine of animals is almost pathognomic for an EG toxicosis. The acute oral toxicity in rats of EGD is also in the same range as EG (6.86 g/kg verse 4 – 10.2 g/kg, respectively).

In conclusion, even though much of the evidence for the metabolic conversion of EGD to EG is somewhat circumstantial in nature, it is still believed to be of sufficient strength to support a conclusion that data from EG can be used for some mammalian toxicity endpoints in lieu of information on EGD. Specifically, the data from EG is needed to assess the potential for EGD to induce reproductive and developmental toxicity. Furthermore, while data from repeat dose studies are available on EGD, its robustness and quality are limited (data are from old studies). Accordingly, in making a hazard assessment of EGD for this endpoint, one should also review information publicly available on EG.

TEST PLAN SUMMARY

CAS No. 111-55-7	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	Y	-	-	Y	Y	N
Biodegradation	Y	Y	-	-	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity ¹	Y	-	Y	-	N	Y	N
Genetic Toxicity – Mutation	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity ¹	Y	-	-	-	-	-	N
Toxicity to Reproduction ¹	Y	-	-	-	-	-	N

1. This endpoint is either completed or supported through the use of data on ethylene glycol used as a surrogate.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained from reputable text book referenced within the Hazardous Substance Data Base (HSDB).

Boiling Point - A value for this endpoint was obtained from reputable textbook referenced within the HSDB.

Vapor Pressure - A value for this endpoint was obtained from reputable textbook referenced within the HSDB.

Partition Coefficient - A value for this endpoint was obtained from reputable textbook referenced within the HSDB.

Water Solubility - A value for this endpoint was obtained from reputable textbook referenced within the HSDB.

Conclusion: All end points have been satisfied by the utilization of data obtained from reference values located in reputable textbooks identified by the HSDB. No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using AOPWIN, a computer estimation modeling program (1).

Stability in Water - This endpoint was filled by data from an abiotic degradation study that followed established guidelines and GLP assurances (OECD TG-111).

Biodegradation - This endpoint was satisfied through a technical argument linking EGD to ethylene glycol. Please see an assessment of this end point in the Ethylene Glycols category of chemicals under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model within EPIWIN.

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models (2). In total, they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint is filled by data from an OECD TG-203 study conducted under GLP assurances.

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from an OECD TG-202 study conducted under GLP assurances.

Toxicity to Aquatic Plants - This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from well-conducted studies using OECD guideline methods and GLP assurances. They are all of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity -	This endpoint is filled by oral exposure data found in a peer-reviewed journal. The study was completed quite some time ago and did not follow an established protocol. The quality of this study was still deemed as “reliable with restrictions” and little would be accomplished by conducting a new study. (The value referenced is similar to that of EG which is used as a surrogate for some endpoints.)
Repeat Dose Toxicity -	This endpoint is filled by data from 2 oral exposure studies (drinking water) identified in peer-reviewed journals. Both had exposure durations of about 130 days. Neither study followed established protocols and both were completed quite some time ago. The quality of these studies was deemed as “reliable with restrictions” as they lacked much detail. However, their main functionality lies in the fact that the observations noted in these studies are consistent with the assumption that the toxicity of EGD is due to its biological transformation to EG. Again data from EG alone should be used when assessing the repeat dose hazard potential of EGD.
Genetic Toxicity Mutation -	This endpoint is filled with a study that followed established guidelines (EEC Annex V Guideline number B.14) and GLP assurances. This study utilized <i>Salmonella typhimurium</i> (strains TA 98, 100, 1535, 1537, and 1538) and <i>Escherichia coli</i> (strain WP2uvrA). The quality of this study was deemed as “reliable without restrictions”.
Aberration -	This endpoint is filled with data from an <i>in vitro</i> study using Chinese hamster ovary (CHO) cells that followed OECD guideline #473 and was conducted under GLP assurances. The quality of this study was deemed as “reliable without restrictions”.
Developmental Toxicity -	This endpoint is filled by data from ethylene glycol, which serves as surrogate chemical. A justification for its use has been provided. Robust summaries on EG for this end point can be found in the Ethylene Glycols category of chemicals being assessed under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.
Reproductive Toxicity -	This endpoint is filled by data from ethylene glycol, which serves as surrogate chemical. A justification for its use has been provided. Robust summaries on EG for this end point can be found in the Ethylene Glycols category of chemicals being assessed under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.
Conclusion:	All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines, or utilized methods that were very similar and scientifically appropriate. The endpoints assessing reproductive and developmental toxicity utilize information available on EG, the presumed metabolite of EGD. Although actual data on EGD are available for assessing systemic toxicity from repeated exposures, it is recommended that data from EG be used as a supplement in evaluating the hazard potential of EGD for this endpoint. In total the data available on EGD or its surrogate (EG) are of sufficient quality to conclude that no additional testing should be performed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for EGD were all obtained from texts references found in the HSDB. These data indicate that EGD is a liquid at room temperature with a relatively low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of actual data, technical arguments based on SAR, and acceptable estimation modeling programs. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that EGD will distribute primarily to soil and water. Results of an OECD TG 111 study demonstrate EGD will readily hydrolyze under basic conditions with a half-life of <2.5 hours. It would be readily anticipated that the ester linkages bonding the two acetate units onto the EG molecule would be rapidly degraded by microbes in the environment. A technical argument is presented discussing this and the readily degradability of the parent ethylene glycol molecule. Its primary use in coatings applications will result in environmental releases that occur primarily through evaporative emissions. EGD is expected to degrade in the atmosphere at a relatively fast to moderate rate with an estimated atmospheric half-life of <3 days.

The potential toxicity of EGD to fish, Daphnia, and algae were determined through well-conducted guideline studies. The results of these studies demonstrated that Daphnia and algae were not sensitive species with both having a NOEC >100 mg/L. However, the LC₅₀ determination in fish was only 40.45 mg/L. Based on these data EGD would be classified as “harmful to aquatic organisms” according to the European Union’s labeling directive but would be classified in a “moderate concern level” according to the U.S. EPA’s assessment criteria. The potential for significant exposures to aqueous environments is unlikely except under accidental conditions and it is noted as being readily biodegradable by wastewater organisms. Interestingly, the LC₅₀ determinations to ethylene glycol in the same species of fish were 53,000; 49,000; and 57,000 mg/L for fry, juvenile, and subadult fish, respectively. The basis of the wide gulf between these values and those observed for EGD is unknown.

The potential to induce toxicity in mammalian species following acute oral exposure is low with an LD₅₀ value in rats of 6.86 g/kg. These data are analogous to those obtained on the parent molecule EG (5.89 – 13.4 g/kg). Data from two repeat exposure studies in rats in which EGD was put into drinking water at levels of 1 – 5% for about 130 days showed evidence of renal toxicity and formation of calcium-oxalate crystals. This finding is analogous to what may be seen following an exposure EG alone. Results from mutagenicity and chromosomal aberration studies indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were assessed through the use of a surrogate chemical ethylene glycol. Numerous studies can be found in the public literature for EG on these latter two endpoints, as well as others. Robust summaries will be available on ethylene glycol under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative. The reproductive toxicity of EG is also undergoing a review by the National Toxicology Program’s Center for the Evaluation of Risks to Human Reproduction (CERHR). The results of this review will also be available to the public.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on EGD that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA, as well as through the use of surrogate data. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to workers and the general population as well as the environment.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

1. **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
2. **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
3. **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
4. **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

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